Breast Surgery Unit
Helsinki University Central Hospital
University of Helsinki
Finland

LOCAL AND REGIONAL RECURRENCES IN BREAST CANCER AND PAGET´S DISEASE OF THE BREAST

Elina Siponen

ACADEMIC DISSERTATION

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Supervised by

Docent Marjut Leidenius

Breast Surgery Unit

Helsinki University Central Hospital

Reviewed by

Professor Vesa Kataja

Department of Oncology

Kuopio University Hospital

Professor Hannu Paajanen

Department of Surgery

Kuopio University Hospital

Opponent

Professor Cornelis van de Velde

Department of Surgical Oncology

Leiden University Medical Center

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2. List of Abbreviations

ALND	Axillary lymph node dissection
AR	Axillary recurrence
BCSS	Breast cancer-specific survival
BCT	Breast-conserving therapy
CI	Confidence interval
DCIS	Ductal carcinoma in situ
EIC	Extensive intraductal component
ER	Oestrogen receptor
HER2	Human epidermal growth factor receptor-2
HR	Hazard ratio
ITC	Isolated tumour cells
LR	Local recurrence
LRR	Local-regional recurrence
MRI	Magnetic resonance imaging
OS	Overall survival
PR	Progesterone receptor
SNB	Sentinel node biopsy
SR	Supraclavicular recurrence

3. Abstract

Aim

The incidence and risk factors of local and regional recurrences after surgical treatment of invasive breast cancer treated with modern adjuvant therapies were evaluated. Another interest was to determine the outcome of surgical treatment in patients with Paget´s disease of the breast, with a special emphasis on sentinel node biopsy and magnetic resonance imaging.

Patients and methods

The study population consisted of 1297 patients with pT1 invasive breast cancer treated with breast-conserving therapy, 755 patients with invasive cancer treated with mastectomy and 1180 patients with invasive cancer and axillary lymph node dissection treated at the Breast Surgery Unit of Helsinki University Central Hospital between the years 2000 and 2005. Also included were 58 patients with Paget´s disease of the breast treated between 1995 and 2006 at the same unit.

Medical files were retrospectively reviewed and analysed. Data on cancer recurrence and survival were collected from hospital records and registries and from the files of the Finnish Cancer Registry. The Finnish Cancer Registry has a coverage approaching 100%.

Results

After breast conservation, the 5-year local recurrence rate was 2.1% in patients with pT1 tumours after a median follow-up of 57 months. Local recurrences were located in the quadrant of the prior breast resection in 63% cases. The most significant risk factor for local recurrence after breast conservation was omission of radiotherapy, HR (hazard ratio) 10.3 [95% CI (confidence interval) 1.9-56.2, p=0.007].

After mastectomy, the 7-year local recurrence rate was 2.9% after a median follow-up of 89 months. In the multivariate model, no independent risk factors emerged for local recurrence. Calculated from the date of detection of the recurrence, the 5-year breast-cancer specific survival was 77.5% and overall survival 59.2% in patients with isolated local recurrence.

After axillary lymph node dissection, the 7-year axillary recurrence rate was 0.7% and supraclavicular recurrence rate 1.3%. No risk factors for axillary recurrence were identified. A vast majority, 86% of patients with supraclavicular recurrence and 50% of patients with axillary recurrence, had concomitant distant recurrences.

Altogether 56 patients with Paget´s disease of the breast (97%) had underlying invasive (31 patients) or in situ carcinoma (25 patients) in the ipsilateral breast. Multifocal or multicentric invasive or in situ carcinoma was detected in 40% of patients with Paget´s disease. The overall mastectomy rate was 76%. The sensitivity of mammography, ultrasound and magnetic resonance imaging for invasive cancer in patients with Paget´s disease was 79%, 74% and 100%, respectively, and for in situ carcinoma 39%, 19% and 44%, respectively.

Conclusions

Local and regional recurrences are rare after breast cancer surgery and modern multidisciplinary treatment, at least during a short follow-up. Paget´s disease is rather frequently associated with peripheral or multicentric cancer. Sentinel node biopsy is recommended in patients with Paget´s disease with invasive cancer or in case of mastectomy. Magnetic resonance imaging may be helpful in patients with Paget´s disease with negative findings in conventional imaging.

4. Introduction

Local recurrence (LR) here is defined as any recurrent cancer detected in the ipsilateral breast after breast conservation or in the ipsilateral thoracic wall after mastectomy. Axillary recurrence (AR) is defined as cancer recurrence in the ipsilateral axillary lymph nodes, and supraclavicular recurrence (SR) as cancer recurrence in the ipsilateral supraclavicular lymph nodes. Regional recurrence includes any cancer recurrence in the ipsilateral lymph node regions (axillary-, supra/infraclavicular- or internal mammary nodes). Any cancer recurrence outside the regional lymph nodes or breast/thoracic wall is considered distant recurrence.

The presence of local-regional recurrence (LRR) increases considerably the risk of developing distant disease (de Bock et al. 2009), and the reduction of LRs improves survival (EBCTCG 2005).

After breast conservation, the incidence of LR is 0.5-1% per year (Millar et al. 2009, Sanghani et al. 2010); and the incidence has declined particularly among younger patients (Cabioglu et al. 2005). Todays´s more effective and frequently used systemic adjuvant therapies and better quality of surgery and pathological assessment translate into fewer LRs. Commonly reported risk factors for LR include young patient age, extensive intraductal component (EIC) and positive resection margins (Voodg et al.1999, Singletary et al.2002, Miles et al. 2011).

Evidently also the biological tumour subtype has an impact on LRs. Particularly the triple negative tumour subtype (Zaky et al. 2011) as well as the HER-2 positive tumour subtype (Lowery et al. 2012) are related to more frequent recurrences. The use of monoclonal HER-2 antibody, trastuzumab, seems to decrease the LRR risk substantially in HER-2-positive cancers (Viani et al. 2007, Kiess et al. 2012).

LRRs after mastectomy, in turn, are related to high histological tumour grade, absence of steroid hormone receptors and young age, but probably the two most important risk factors are large tumour size and positive nodal status (Taghian et al. 2004, Nielsen et al. 2006, Taras et al. 2011). Although LRs after mastectomy are associated with dismal survival, more favourable survival rates have been reported in patients with isolated LR, that is, without concomitant regional or distant recurrence (Chagpar et al. 2004, Chen et al. 2009).

ARs and SRs are also rare, 0.6-1% and 0.6-1.8%, respectively, at five years after axillary lymph node dissection (ALND) (Fredriksson et al. 2002, Grills et al. 2003, Livi et al. 2006, Gentilini et al. 2007). Adjuvant radiotherapy reduces substantially the risk for regional recurrence (Truong et al.

2009, Rowell et al. 2009), but whether all node-positive patients should receive post-mastectomy radiotherapy or radiotherapy to the regional nodal basins remains controversial.

Paget´s disease of the breast is a rare condition, representing approximately 1-3% of all breast cancers. It is often associated with invasive or intraductal breast cancer (Kollmorgen et al. 1998, Kawase et al. 2005). The underlying malignancy is often multicentric or multifocal (Kothari et al. 2002, Kawase et al. 2005) and traditionally, the treatment has been mastectomy. However, similar survival and local control have been reported with breast-conserving surgery in selected patients (Marshall et al. 2003, Kawase et al. 2005). Because of the high number of false negatives in mammography, breast magnetic resonance imaging (MRI) is frequently recommended in Paget´s disease, particularly when considering breast conservation (Morrogh et al. 2008, Dominici et al. 2012).

The aim of the present retrospective study was to evaluate the incidence and risk factors of local and regional recurrence after surgery and modern adjuvant treatments in invasive breast cancer. A further aim was to evaluate the treatment and outcome of patients with Paget´s disease of the breast and to determine whether an indication exists for breast MRI in these patients. In addition, the role of sentinel node biopsy (SNB) in patients with Paget´s disease was examined.

5. Review of the Literature

5.1 Breast cancer incidence and survival

Breast cancer is the most common cancer in women worldwide. The annual incidence in Finland in 2011 was 4869. In Finland, the predicted breast cancer-specific five-year survival rate for patients under follow up from 2007 to 2009 is 89%. The incidence is increasing and more than 5100 new breast cancers are estimated to be found in the year 2020 (Pukkala et al. 2011).

5.2 Histological subtypes of breast cancer

Histological subtypes of breast cancer are classified according to the World Health Organization´s classification of tumours. The most common histopathological types are ductal and lobular carcinoma, representing 40-75% and 5-15% of all invasive breast cancers, respectively. Other subtypes are more rare, including tubular carcinoma (2% of breast carcinomas), cribriform carcinoma (0.3-0.8%), medullary carcinoma (<1%), mucinous carcinoma (2%), neuroendocrine carcinoma (<1%), papillary/micropapillary carcinoma (0.9-2%), apocrine carcinoma (4%) and metaplastic carcinoma (0.2-0.5%). Ductal carcinoma in situ (DCIS) is defined as a neoplastic proliferation of epithelial cells characterized by cytological atypia and tendency for progression to invasive breast cancer (Lakhani et al. 2012). Unlike invasive breast cancer, DCIS does not grow through the basement membrane of the lactiferous duct and therefore cannot metastasize.

5.3 Local-regional treatment and survival in breast cancer

The first widely recognized theory of spread of breast cancer was described by Dr. William Halsted. The “Halstedian” theory considers breast cancer a local disease that will spread from the primary site through lymphatics to lymph nodes, eventually developing into distant metastases. This approach advocates radical local-regional treatment.

Another theory arose since many women developed distant metastases despite aggressive local treatment. Dr. Bernard Fisher and others suggested that breast cancer is primarily a systemic disease, and if distant metastases occur, they were present already at the time of diagnosis. This hypothesis emphasizes the role of systemic treatment over local treatment. Some randomized clinical trials supported this systemic theory since the improvement of local control seemed to provide no survival benefit (Fisher et al. 2002). However, increasing evidence has since emerged strongly labelling this systemic theory as incorrect. Firstly, mammographic screening reduces breast cancer mortality; thus, earlier diagnosis can prevent distant metastases (Berry et al. 2005, Punglia et al. 2007). Secondly, and most importantly, the EBCTCG meta-analysis indicated that adequate local control can improve survival by demonstrating that for every four LRs prevented one breast cancer death can be avoided (EBCTCG 2005).

A third theory introduced by Samuel Hellman and colleagues from the United States assumed that breast cancer comprises “a heterogeneous spectrum of malignant proclivities” (Hellman 1994). This spectrum hypothesis suggests that breast cancer is a variety of tumours of different metastatic capabilities. Clinical data reveal that with increasing tumour size and nodal metastases this spectrum becomes weighted toward greater malignant capacity, but each clinical group itself is heterogeneous (Heimann and Hellman 2000).

Today, gene expression profiling-derived biological breast cancer subtypes are being studied intensively. Generally, at least four different biological subtypes are identified comprising Luminal A, Luminal B, HER2-enriched and Basal types. These biological subtypes can be classified also according to their expression of immunohistochemical markers such as oestrogen receptor (ER), progesterone receptor (PR) and HER2/neu receptor. Luminal A is typically ER+ and/or PR+, HER2-, Luminal B is ER+ and/or PR+, HER2+, Basal-like (ER-, PR-, HER2-), i.e. so-called triple-negative and HER2-enriched (HER2+, ER-,PR-).

In the future, more specific knowledge of cancer biology may help to detect more individualized models of dissemination patterns in breast cancer (Sihto et al. 2011). Recognizing the patients at risk of systemic disease, based on molecular features rather than tumour size itself or nodal stage, might help to target the adjuvant systemic treatment more individually. Patients whose risk for metastatic disease is estimated to be low, might benefit more from good local disease control.

5.4 Aims of surgical treatment of breast cancer

The aim of surgical treatment is to remove the breast tumour and metastatic axillary lymph nodes, thus preventing LRRs and improving survival. Surgery enables pathological assessment and staging of the tumour, providing important knowledge regarding prognosis and tailoring of adjuvant treatments. Moreover, the accuracy of axillary nodal staging is dependent on the number of examined lymph nodes, that is, on the quality of surgery and pathological assessment (Schaapveld et al. 2006).

On the other hand, patients with a limited life expectancy or severe comorbidities might not benefit from any surgery.

Most women with breast cancer survive and have a good or even excellent prognosis so the quality of life after treatment is extremely important. Mastectomy is associated with impaired quality of life regarding body image. Also functional outcome may be worse after mastectomy, with constrictive scarring, compared with breast-conserving procedures.

Axillary surgery is also associated with acute and long-term morbidity, which, however, is less common in patients with SNB than with ALND (Mansel et al. 2006).

Therefore, an important aim of surgery is to tailor each treatment individually, in agreement with the patient, taking into account both local-regional disease control and the aesthetic and functional outcomes.

5.5 History of breast cancer surgery

Radical mastectomy was described simultaneously by Halsted and Meyer in the early 1900s. Based on the hypothesis by William Halsted (described earlier), it consisted of removing not only the breast glandular tissue but also the pectoralis major and minor muscles with the axillary lymph nodes. In 1937, the surgeon Geoffrey Keynes demonstrated that less radical surgery was as effective, and both modified radical and simple mastectomies were shown to have similar outcomes to radical mastectomy. However, the extent of axillary surgery remained the same.

In the 1930s, Finnish Professor Sakari Mustakallio developed and started to perform breast-conserving surgery, but it was not until the 1970s that this more conservative approach to breast surgery began to gain acceptance. When the results of the randomized studies of Drs. Bernard Fisher and Umberto Veronesi reported similar survival in patients treated either by breast-conserving surgery and radiotherapy or mastectomy, breast conservation became a routine treatment option in breast cancer surgery. However, ALND remained the gold standard in axillary staging. During the 1990s SNB was introduced and became a routine procedure for axillary staging in patients without clinical evidence of axillary lymph node metastases.

5.6 Breast conservation

Breast-conserving surgery was initially recommended only to patients with small (<2 cm) unifocal tumours with a low risk of lymph node metastases. Later, breast conservation was shown to also be a safe option for patients with tumours up to 5 cm and for those with axillary lymph node metastases (Litiére et al. 2012). Multifocal and particularly multicentric cancer has been considered a contraindication for breast conservation. However, it seems to be a feasible and safe option in selected patients when good aesthetic outcome and tumour-free margins are achieved (Gentilini et al. 2009).

Neoadjuvant treatment is a treatment option for patients who desire breast conservation, but the tumour is too large for that approach. Neoadjuvant treatment may decrease the size of the tumour, enabling breast conservation. Breast-conserving surgery after neoadjuvant treatment seems to have comparable locoregional control as “upfront surgery” (Mittendorf et al. 2013).

Oncoplastic techniques in breast conservation may help to preserve the breast with a good cosmetic result, especially in cases in which the size or location of the tumour is too challenging for conventional wide local excision. Oncoplastic techniques are gaining increasing popularity and are widely used also by breast cancer surgeons without prior plastic surgery training.

5.7 Mastectomy

Mastectomy was the standard treatment for all breast cancer patients until the 1980s. Today, mastectomy is still recommended for many patients with a tumour size too large to allow breast-conserving surgery with acceptable aesthetic outcome or it is performed due to patient preference. In case of inflammatory cancer, mastectomy is indicated after neoadjuvant treatment. Another indication for mastectomy is when radiotherapy is contraindicated, as for example if the patient has received mantle field radiation for Hodgkin´s disease.

In young patients, aesthetic outcome is particularly important, but at the same time they face a higher risk than older women for LR after breast conservation (Elkhuizen et al.1998, Beadle et al. 2009), and mastectomy could be the safest treatment option. Especially patients with a genetic predisposition for breast cancer, like BRCA1 or BRCA2 mutation carriers, have a high risk for recurrent or new primary disease during the lifetime. This risk could be minimized by leaving as little residual breast tissue as possible. This often involves bilateral mastectomy. Also the follow-up after surgery may be more challenging because of the denser breast tissue in young women. However, young patients are usually good candidates for either immediate or delayed breast reconstruction.

Breast reconstruction seems to be safe (Veronesi et al. 2011) and is often feasible also for older women depending on their preference and their general health.

5.8 Axillary surgery

ALND has been the gold standard in axillary staging. A diagnostic ALND includes Berg levels I and II (lymph nodes lateral to and underneath the pectoralis minor muscle). Berg level III includes lymph nodes medial to the pectoralis minor muscle. These should be included in dissection at least in patients with overt axillary metastases. The accuracy of axillary nodal staging is dependent on the number of examined nodes (Schaapveld et al. 2006). Traditionally, ALND has been considered adequate if at least ten lymph nodes have been examined. However, a higher number of examined nodes facilitates distinguishing between nodal stages; in particular, the proportion of tumours with more than four positive nodes increases concomitantly with an increasing number of reported nodes, i.e. it includes stage shifting (Schaapveld et al. 2004). Nevertheless, the number of examined lymph nodes depends not only on the quality of surgery but also on the quality of pathology.

According to a meta-analysis, ALND provides an absolute 5% survival benefit in breast cancer patients (Orr 1999). However, this conclusion has been criticized since the treatment modalities as well as the patient characteristics included in the meta-analysis differ from the circumstances of today. ALND is associated with acute and long-term morbidity such as post-operative seroma, loss of sensation and pain in the axilla and upper arm, disturbance of shoulder function and most importantly lymphoedema (Nagel et al. 2003).

Mammography screening and improved diagnostics in general facilitate detection of breast cancers at an early stage without axillary lymph node involvement (Joensuu et al. 2004). ALND is therapeutic only in patients who are node-positive. Performing ALND in all breast cancer patients leads only to an unnecessary morbidity and overtreatment in patients without metastatic nodes.

The status of the axilla provides essential prognostic information that cannot be obtained without surgery. Currently, the routine ultrasound assessment of the axilla in combination with needle biopsy can detect a positive axillary node in approximately 80% (Houssami et al. 2011) of node-positive patients. The benefit of the ultrasound assessment of the axilla is avoiding SNB when axillary lymph node metastases are detected already preoperatively. However, neither axillary ultrasound nor other imaging modalities are sufficiently sensitive to exclude axillary lymph node metastases. Compared with ALND, SNB enables staging the axilla accurately, with a faster recovery and less long-term morbidity (Mansel et al. 2006).

Until recently, ALND has been the routine treatment in sentinel node-positive patients. However, only about 40% of the patients with positive sentinel nodes have more metastatic nodes detected in ALND (van la Parra et al. 2011). The risk of finding more metastatic nodes in ALND is even less in patients with only isolated tumour cells (ITCs) or micrometastases (0.2-2 mm of tumour deposit) found in their sentinel nodes (van la Parra et al. 2011). Also primary tumour-related factors, such as tumour size or multifocality, influence the probability of finding more metastatic nodes in ALND after positive SNB (van la Parra et al. 2011).

Therefore, predictive tools to estimate the likelihood of additional axillary metastases after tumour-positive SNB in individual patients have been developed. The first one was introduced by the Memorial Sloan-Kettering Cancer Center (Van Zee et al. 2003). Since then, other centres have developed similar nomograms, as the estimation is most accurate at the centre where the tool is developed. An ideal predictive tool might be international and multi-institutional such as the one developed by Meretoja et al. (2012).

To evaluate the need for ALND after tumour-positive SNB, a prospective randomized trial, ACOSOG Z0011, was conducted (Giuliano et al. 2011). The trial included patients with clinical T1-2N0M0 breast cancer treated with breast conservation and whole-breast radiotherapy. The patients were randomized either to ALND or observation after detection of one or two tumour-positive sentinel nodes in SNB. No difference in survival or in recurrence rates were observed during a follow-up of 6.3 years. However, the study has some limitations including the relatively short follow-up time and a selected study population. It is also noteworthy that a marked proportion of the study patients had micrometastases only, particularly in the observation group. Furthermore, the results cannot be extrapolated to patients with mastectomy.

Another randomized trial, AMAROS, compares ALND with axillary radiotherapy in patients with positive sentinel lymph nodes (Straver et al. 2010). Preliminary results of the trial show that “absence of knowledge regarding the extent of nodal involvement in the axillary radiotherapy arm appears to have no major impact on the administration of systemic adjuvant therapy” (Straver et al. 2010). The results of this study regarding ARs and survival may be practice-changing in patients with positive SNB. Of particular interest is also the possible difference in morbidity between the two treatment arms.

5.9 Local and regional recurrences in breast cancer

One aim of routine controls after primary breast surgery and treatment is to detect LRs and regional recurrences at an early stage. Detection of asymptomatic local-regional recurrences carries a survival benefit compared with symptomatic detection (Lu et al. 2009). The majority of asymptomatic LRRs are detected during routine visits, while symptomatic LRRs are more often detected by patients between routine visits (Geurts et al. 2012). LRs following mastectomy and immediate breast reconstruction occur most often in the skin or subcutaneous tissue and are usually readily detected in clinical examination (Langstein et al. 2003). In a meta-analysis in 2010 no significant difference emerged in the rates of LRs between patients with mastectomy and patients with mastectomy and immediate breast reconstruction (Lanitis et al. 2010). After detection of LRR, in clinical examination or on imaging, usually an ultrasound-guided needle biopsy is performed to confirm the diagnosis.

The prevention of LR and regional recurrence is essential in breast cancer treatment. LR or regional recurrence, even when isolated without distant disease, is related to worse survival. Approximately one-half of the patients treated in the 1980s and the 1990s survived for five years after detection of isolated LR after mastectomy or BCT (Wapnir et al. 2006, Nielsen et al. 2006). A similar five-year survival of 50% was detected in patients with isolated AR treated from 1989 to 2003 (Konkin et al. 2006).

The EBCTCG overview demonstrated a survival benefit after a better local-regional disease control with radiotherapy in patients with breast conservation, and also in node-positive patients with mastectomy (2005). The reduction of LRs does not translate into better survival in all breast cancer patients. However, LRs cause a lot of anxiety, morbidity and costs, even in patients without a survival disadvantage.

According to the randomized studies, the incidence of LR after breast conservation combined with radiotherapy is 9-14% at 20 years (Veronesi et al. 2002, Fisher et al. 2002) and is nowadays approximately 0.5%/year (Millar et al. 2009, Sanghani et al. 2010). The risk factors for LR after BCT have been studied extensively. After BCT, positive resection margins leads to more LRs (Singletary 2002), and therefore, the resection margins should be negative. However, extensive negative margins (>2 mm) seem to offer no benefit in reducing LRs relative to negative margins of less than 2 mm (Houssami et al. 2010, Groot et al. 2011). An International Expert Panel endorses “tumour not touching the ink “ as standard of an adequate negative margin in patients with invasive cancer (Kaufman et al. 2010). Extensive intraductal component (EIC) is a risk factor for LR, and perhaps wider margins should be recommended in cases with EIC (Voogd et al. 1999).

Young age is strongly related to more LRs after BCT (Elkhuizen et al. 1998). However, it seems that the decrease in the LR rate with modern multidisciplinary treatment is especially seen in women aged under 50 years (Cabioglu et al. 2005). LRs after BCT may be more common in patients with a genetic predisposition to breast cancer such as BRCA1 or BRCA2 mutation carriers (Garcia-Etienne et al. 2009).

The role of radiotherapy is essential in reducing LRs after BCT. Whole-breast adjuvant radiotherapy reduces LRs by two-thirds, and a booster dose to the resection site further decreases the LR rate, especially in premenopausal patients (Jones et al. 2009). The omission of radiotherapy is related to more recurrences, a 5-year LR rate of 26% without and 7% with adjuvant radiotherapy has been reported after breast conservation (EBCTCG 2005).

Tumour-related histological and biological factors influence LRRs after both BCT and mastectomy. High histological tumour grade or absence of hormone receptors is correlated with more recurrences regardless of the type of surgery (Jones et al. 2009, Taras et al. 2011). Following both BCT and mastectomy, a high LRR rate is associated with triple-negative cancer (i.e. no positive steroid hormone receptors and HER2-), thus lacking targets for treatment (Zaky et al. 2011, Adkins et al. 2011). Prior to modern treatments, patients with HER2-positive cancers were at higher risk of LRR despite the type of surgery (Lowery et al. 2012), but the use of monoclonal antibody, trastuzumab, in combination with conventional chemotherapy provides a significant reduction in LRRs (Viani et al. 2007, Kiess et al. 2012). In general, the risk of LR is reduced by using systemic adjuvant treatment such as endocrine therapy in patients with ER-positive cancer or adjuvant chemotherapy in patients under 70 years of age (EBCTCG 2005b).

The incidence of LRs after mastectomy has varied from 2.3% to 10.2% at 20 years (Fisher et al. 2002, Veronesi et al. 2002), which translates to less than 0.5%/year. In a more recent study, a 10-year LR rate of 5.7% was detected in patients with mastectomy when no radiotherapy was used (Botteri et al. 2012).

Besides the tumour-related histopathological and immunohistochemical factors mentioned above, large tumour size and positive axillary lymph node status correlate with more LRs after mastectomy. A 5-year LR rate of 18% after mastectomy was noted in patients with T3 or T4 tumours compared with 4% in the whole study group when only 11% of the study patients received adequate radiotherapy (Bijker et al. 1999). The EBCTCG meta-analysis reported a 5-year LR rate of 6% in node-negative patients, 16% in patients with one to three positive nodes and 26% in patients with more than four positive lymph nodes, all without post-mastectomy radiotherapy (EBCTCG 2005a). Post-mastectomy radiotherapy significantly reduces LRs after mastectomy in all patients but the absolute gain is larger in high-risk patients (EBCTCG 2005a).

Higher LR rates have been observed in young patients, not only after breast conservation, but also after mastectomy (Yildirim and Berberoglu 2007). Young age was an independent risk factor for LRR after mastectomy when post-mastectomy radiotherapy was not given (Sharma et al. 2010). The significance of post-mastectomy radiotherapy in young patients was demonstrated in two studies (Beadle et al. 2009, Liukkonen et al. 2011). Liukkonen and colleagues (2011) reported a LR rate of 1% after post-mastectomy radiotherapy compared with 15% without radiotherapy in patients under 35 years during a median follow-up of 6.5 years. Accordingly, Beadle et al. (2009) found a 10-year LR rate of 12.5% without post-mastectomy radiotherapy in patients under 35 years compared with 7.0% when post-mastectomy radiotherapy was used, although the patients with post-mastectomy radiotherapy had worse prognostic features.

After ALND, both ARs and SRs are rare, 0.6-1.0% and 0.6-1.8%, respectively, over a 5-year follow-up (Fredriksson et al. 2002, Grills et al. 2003, Livi et al. 2006, Gentilini et al. 2007). According to a meta-analysis, ARs are also very rare after negative SNB, usually less than 0.5% during a median follow-up of 34 months after surgery (van der Ploeg et al. 2008).

The recurrences in regional lymph nodes after breast conservation may be more common in patients with high-risk tumours such as ER-negative or HER2-positive tumours or tumour size larger than 2 cm (Botteri et al. 2009). More ARs have been reported in young patients as well as in those with medially located tumours (Shen et al. 2012). The quality of surgery is important and the high number of examined nodes correlates not only with better accuracy in nodal staging (Schaapveld 2006) but also with the risk of leaving residual disease. The relative risk for AR was 5.5 for patients under 50 years with less than seven examined lymph nodes compared with patients with seven or more nodes found in the axillary lymph node specimen (Voogd et al. 2001). Also the high number or the high proportion of metastatic axillary lymph nodes is associated with more RRs (Grills et al. 2003, Truong et al. 2009).

Radiotherapy to the regional nodal basins reduces regional recurrences (Voogd et al. 2001, Truong et al. 2009) but much controversy exists particularly regarding patients with 1-3 positive lymph nodes. In the MA20 trial, regional radiotherapy after ALND was beneficial in patients with BCT and whole-breast radiotherapy (Whelan 2011). On the other hand, the Z0011 trial suggests it is safe to leave patients with positive sentinel node without regional radiotherapy and also without ALND when whole-breast radiotherapy after breast conservation is used (Giuliano et al. 2011).

5.10 Paget´s disease of the breast

Paget´s disease of the breast is a rare condition diagnosed in approximately 1-3% of all breast cancer cases. In 1874, Sir James Paget described changes in the nipple preceding diagnosis of breast cancer. Paget´s disease usually appears as an eczematoid change as erythema or scaling of the nipple and can be frequently mistaken as being a benign condition such as dermatitis or mastitis. Accordingly, the diagnosis is often delayed. A skin biopsy of the suspicious area should be taken because the diagnosis is histological and consists of finding typical large, round and ovoid pleomorphic “Pagetoid” cells in the nipple epidermis.

Two main theories regarding the pathogenesis of Paget´s disease of the breast are recognized. The first, “in situ transformation theory”, considers Paget cells to be of intraepidermal origin with the potential to become malignant. The second, “epidermotrophic theory”, suggests that Paget cells originate from intraductal cancer and then migrate up to the nipple. The majority of patients with Paget´s disease of the breast have underlying in situ or invasive cancer (Kothari et al. 2002), supporting the epidermotrophic theory, but some patients present with only Paget cells in the nipple epidermis (Chen et al. 2006), supporting the “in situ transformation” theory.

The underlying in situ or invasive carcinoma in patients with Paget´s disease of the breast is often multifocal or multicentric (Kothari et al. 2002, Kawase et al. 2005). Accordingly, mastectomy was previously recommended in these patients. However, breast-conserving surgery seems to be a safe option for many patients with this condition (Dominici et al. 2012). Moreover, in some institutions, breast conservation is recommended as the first choice of treatment to all Paget´s patients (Caliskan et al. 2008).

Patients often have false-negative findings in mammography (Bijker et al. 2001, Kothari et al. 2002, Morrogh et al. 2008), which may be due to the high amount of DCIS or multifocality related to Paget´s disease. Therefore, the role of MRI in patients with Paget´s disease has been investigated. Morrogh et al. (2008) found an additional evaluation with MRI helpful in identifying the underlying malignancy in Paget´s patients with negative mammography.

The role of SNB in Paget´s patients has been controversial. A study from Memorial Sloan-Kettering Cancer Center as well as a study from Milan recommend considering SNB in all patients with Paget´s disease even after negative findings in breast imaging (Sukumvanich et al. 2007, Caliskan et al. 2008). Another study by Laronga et al. (2006) suggests that the patients with Paget´s disease of the breast should be treated similarly to any other patient with DCIS or invasive breast cancer with respect to SNB.

Due to the rarity of Paget´s disease of the breast, the number of patients in clinical studies is small. This makes it difficult to evaluate the outcome of various surgical treatment options in this patient group.

6. Study Hypotheses

1. Local and regional recurrences are rare after breast cancer surgery and modern multidisciplinary treatment.
2. Selective use of breast MRI and sentinel node biopsy is useful in Paget´s disease of the breast.

7. Patients and Methods

This work was conducted at the Breast Surgery Unit of Helsinki University Central Hospital. Study I included 1297 patients with pT1 invasive breast cancer treated with breast-conserving surgery between February 2001 and August 2005. Study II included 755 patients with invasive cancer treated with mastectomy between January 2000 and December 2003. Study III included 1180 patients with invasive cancer and ALND between January 2000 and December 2003. Study IV included 58 patients with Paget´s disease of the breast treated between April 1995 and December 2006.

Patients with distant metastases at initial diagnosis as well as patients receiving neoadjuvant treatment were excluded from the study. The study protocol was approved by the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital.

7.1 Surgery

Breast and axillary surgery was performed or supervised by expert breast surgeons. In patients with breast conservation, a wide local tumour excision was performed aiming at 1-2 cm free lateral margins and including the pectoral fascia and usually a slice of the overlying skin of the resected tissue. A second operation (usually mastectomy) was performed whenever the resection margins were involved or close (<3 mm). However, free margins of 10 mm were usually required whenever cancer was multifocal with multiple satellite foci or included EIC. Patients who underwent a second breast resection due to close or positive margins were still included in Study I, whereas those who were ultimately treated with mastectomy were not.

Before January 2000, all patients with invasive or microinvasive cancer underwent ALND. Patients with DCIS underwent partial level I ALND in connection with mastectomy. No axillary surgery was performed on patients with pure DCIS and breast conservation (Study IV, Table 6).

From January 2000 to May 2000, all patients who had a SNB underwent ALND regardless of the findings at the SNB. From June 2000 onwards, SNB was performed on patients who had clinically node-negative, radiologically unifocal breast cancer with the largest tumour diameter $\leq$3 cm as evaluated with a breast ultrasound examination. In these patients, axillary lymph node dissection was omitted whenever the SNB was negative. SNB was performed using preoperative lymphoscintigraphy and intraoperative identification of the sentinel nodes with a gammaprobe and a blue dye.

Six patients included in Study IV with pure DCIS underwent SNB, with negative findings. In Study IV level I and II ALND was performed on two patients with microinvasive DCIS, both with invasive cancer as the preoperative diagnosis. One of these two patients had a lymph node metastasis in her ALND specimen. Five patients with DCIS, including a third patient with microinvasive DCIS, underwent partial level I lymph node dissection (Study IV, Table 6).

Patients with cancer-containing sentinel nodes underwent ALND, except those 15 patients included in Study I who had sentinel node micrometastases or isolated tumour cells (ITCs) and one 95-year-old patient with Paget's disease (Study IV). Level I and II axillary lymph nodes were dissected when clearance of the axillary content was done. The level III nodes were harvested whenever clinically suspicious axillary nodes were present at level II or III.

In Study II, the median number of histologically examined axillary lymph nodes was 3 (range, 1 to 11) in patients who underwent a SNB only and 16 (range, 6 to 52) when ALND with or without a SNB was carried out. In Study III, the median number of lymph nodes examined by the pathologist was 15 (range 6-52), including also sentinel lymph nodes in patients with successful SNB.

7.2 Histopathology

The breast surgery specimens were oriented by the surgeon and sent unfixed to the pathology laboratory. The primary tumour diameter, presence of an EIC or multifocality, histological tumour type, histological tumour grade, ER- and PR status, HER2 amplification status and the proliferation index MIB-1 were assessed by specialized breast pathologists. The ER- and PR status and MIB-1 were assessed using immunohistochemistry. HER2 expression was evaluated using immunohistochemistry, and whenever immunohistochemistry was considered positive (2+ or 3+ on a scale from 0 to 3+), the HER2 status was confirmed with chromogen in situ hybridization (van de Vijver et al. 2007). The histological classification and grading were based on the World Health Organization (WHO) classification of tumours (Sobin et al. 2009).

Sentinel nodes were sent to the pathology laboratory separately from the primary tumour for frozen section analysis. Lymph nodes found in axillary clearance specimens were wholly embedded in paraffin when <5 mm in diameter. When the lymph node size exceeded 5 mm, one representative complete section of the node was embedded in paraffin. Tumour deposits were classified as micrometastases when ≤2 mm in diameter and as ITCs when ≤0.2 mm in diameter. When multiple cancer deposits were found in sentinel nodes, the longest diameter of the largest tumour deposit was recorded as the size of the metastasis. The assessment of sentinel node and ALND specimens is described in detail in a previous study (Leidenius et al. 2010).

Table 1. Patient and tumour characteristics.

Study I: 1297 patients with pT1 invasive breast cancer treated with breast conservation

Study II: 755 patients with invasive cancer treated with mastectomy

Study III: 1180 patients with invasive cancer and ALND

	Study I	**Study II**	**Study III**
	N (%)	**N (%)**	**N (%)**
Variable			
Age at diagnosis (years)			
<40	35 (3)	47 (6)	53 (5)
40-54	445 (34)	242 (32)	426 (36)
55-70	623 (48)	245 (33)	448 (38)
>70	194 (15)	221 (29)	253 (21)
Histological T-stage			
pT1		345 (46)	
pT1a	54 (4)		42 (4)
pT1b	398 (31)		161 (14)
pT1c	845 (65)		500 (42)
pT2		322 (43)	404 (34)
pT3		50 (7)	36 (3)
pT4		36 (4)	35 (3)
NA		2 (<1)	2 (<1)
Axillary lymph node status			
pN0 or N0 (i+)	920 (71)	341 (45)	460 (39)
pN1mi	139 (11)	33 (4)	104 (9)
pN1	186 (14)	220 (29)	384 (32)
N2-N3	49 (4)	160 (21)	232 (20)
NA	3 (<1)	1 (<1)	
Extensive intraductal component			
Absent	1167 (90)	663 (88)	
Present	130 (10)	92 (12)	
Tumour multifocality			
No	1192 (92)	237 (31)	
Yes	104 (8)	515 (68)	
NA	1	3 (<1)	

Histological grade			
1	501 (39)	170 (22)	347 (29)
2	600 (46)	322 (43)	510 (43)
3	184 (14)	247 (33)	302 (26)
NA	12 (1)	16 (2)	21 (2)
Histological type			
Ductal	811 (63)	425 (56)	665 (56)
Lobular	253 (19)	210 (28)	331 (28)
Other	233 (18)	119 (16)	184 (16)
Tumour ER content			
Positive	1178 (91)	615 (81)	1007 (85)
Negative	115 (9)	133 (18)	163 (14)
NA	4 (<1)	7 (<1)	10 (<1)
Tumour PR content			
Positive	951 (73)	449 (59)	761 (65)
Negative	341 (26)	299 (40)	409 (35)
NA	5 (<1)	7 (<1)	10 (<1)
MIB-1 proliferation index			
Very low or low	823 (63)	358 (48)	
Medium	252 (19)	116 (15)	
High	206 (16)	160 (21)	
NA	16 (<2)	121 (16)	
HER2 amplification			
Absent	1051 (81)	581 (77)	929 (79)
Present	68 (5)	96 (13)	136 (11)
NA	178 (14)	78 (10)	115 (10)

Abbreviations: NA = not available, ER = oestrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor-2, MIB-1 = antibody against Ki-67

Table 2. Tumour characteristics of 56 patients with Paget´s disease of the breast and in situ or invasive carcinoma (Study IV).

	DCIS (N=25)	Invasive cancer (N=31)
Multicentric or multifocal tumours		
No	18 (72%)	13 (42%)
Yes	5 (20%)	18 (58%)
Missing data	2 (8%)	0
Tumour location		
Peripheral	4 (16%)	12 (68%)
Central	17 (68%)	5 (16%)
Peripheral and central	4 (16%)	13 (42%)
Missing data	2 (8%)	1 (3%)
Histological T stage		
Tis	22 (88%)	0
Tis microinvasive	3 (12%)	0
T1	0	18 (58%)
T2	0	10 (32%)
T3-T4	0	3 (10%)
Axillary lymph node status		
NX	12 (48%)	0
N0	12 (48%)	13 (42%)
N1mi	0	2 (6%)
N1	1 (4%)	11 (36%)
N2	0	5 (16%)

DCIS = ductal carcinoma in situ, NX= nodal staging not performed, N1m=micrometastases

7.3 Radiotherapy

Radiotherapy to the ipsilateral breast after breast-conserving surgery was given using a linear accelerator to a cumulative dose of 50 Gy in 25 fractions. Premenopausal women received a booster dose of 10-16 Gy given in five to eight fractions to the tumour bed. Other indications for a booster dose consisted of close resection margins and presence of lymphovascular invasion. The whole breast was treated from two tangential fields.

In general, post-mastectomy radiotherapy was given to patients who had a large primary tumour (pT3 or pT4) and to patients who had axillary lymph node-positive cancer. Radiotherapy was based on computer-based dose planning and was given with a linear accelerator with 2 Gy daily fractions, five fractions per week. The cumulative dose to the thoracic wall and the regional node basins was approximately 50 Gy. The ipsilateral thoracic wall, including the surgical scar, was irradiated with electrons from an anterior field to minimize the doses delivered to the heart and the ipsilateral lung. Axillary, supra- and infraclavicular, and often also parasternal nodes were included in the target volume in all node-positive patients during 2000 and 2001. During 2002 and 2005 nodal radiotherapy was recommended for patients with more than one macrometastatic axillary lymph node.

Nevertheless, adjuvant radiotherapy was administered based on the patient and disease characteristics at the discretion of the treating physician.

7.4 Systemic adjuvant therapy

Systemic adjuvant treatment was selected based on the patient and disease characteristics. In general, women with node-positive disease and those considered to have moderate- to high-risk node-negative disease were treated with systemic adjuvant therapy. Patients <65 years of age with moderate- to high-risk cancer, node-negative or node-positive, received adjuvant systemic chemotherapy. The chemotherapy regimens used usually included an anthracycline (usually epirubicin as a component of FEC [fluorouracil, epirubicin, cyclophosphamide]) or a taxane (usually docetaxel), or both, and usually consisted of a total of six cycles administered at three-week intervals. A few patients with HER2-positive breast cancer received trastuzumab concomitantly with chemotherapy within the context of a clinical trial (Joensuu et al. 2006), that is, 15 patients in Study I, four patients in Study II and 28 patients in Study III.

Premenopausal women with ER- and/or PR-positive cancer received tamoxifen and postmenopausal women either tamoxifen or an aromatase inhibitor for five years. Hormonal therapy was initiated after chemotherapy.

None of the patients received neo-adjuvant systemic therapy.

Table 3. Treatment of the 1297 patients with pT1 invasive breast cancer treated with breast conservation (Study I).

Treatment	N (%)
Breast surgery	
Breast-conserving surgery	1297 (100)
Axillary surgery	
None	3 (<1)
SNB	807 (62)
SNB + ALND	398 (30)
ALND due to unsuccessful SNB	53 (4)
ALND without SNB	48 (4)
Radiotherapy	
None	42 (3)
Breast only, no booster dose	899 (69)
Breast only, booster dose	353 (27)
Breast + regional lymph nodes	222 (17)
NA	3 (<1)
Systemic treatment	
None	449 (35)
Endocrine therapy	495 (38)
Chemotherapy	71 (5)
Endocrine and chemotherapy	276 (21)
Trastuzumab + other systemic therapy	15 (1)
NA	2 (<1)

Abbreviations: SNB = sentinel node biopsy, ALND = axillary lymph node dissection, NA = not available

Table 4. Treatment of patients in Studies II (755 patients with invasive cancer and mastectomy) and III (1180 patients with invasive cancer and ALND).

		Study II	Study III
		N (%)	N(%)
Axillary surgery	SNB	106 (14)	
	SNB and ALND	153 (20)	411 (35)
	ALND after unsuccessful SNB	4 (<1)	34 (3)
	ALND	492 (65)	735 (62)
Breast surgery	Breast-conserving surgery	554 (47)	
	Mastectomy	755 (100)	626 (53)
Radiotherapy			
pN0	None	281 (82)	194 (42)
	Breast/Thoracic wall only	51 (15)	255 (56)
	Breast/Thoracic wall and regional lymph nodes	6 (2)	11 (2)
	Regional lymph nodes only	0	0
	Not available	3 (1)	0
pN1 or pN1mi	None	57 (23)	64 (13)
	Breast/Thoracic wall only	12 (5)	61 (13)
	Breast/Thoracic wall and regional lymph nodes	180 (71)	363 (74)
	Regional lymph nodes only	3 (1)	0
	Not available	1 (< 1)	0
pN2 or pN3	None	21 (13)	28 (12)
	Breast/Thoracic wall only	6 (4)	12 (5)
	Breast/Thoracic wall and regional lymph nodes	132 (83)	190 (82)
	Regional lymph nodes only	1 (< 1)	2 (<1)
Systemic adjuvant treatment			
pN0	None	133 (39)	226 (49)
	Endocrine therapy	124 (36)	134 (29)
	Chemotherapy	39 (11)	41 (9)
	Endocrine and chemotherapy	44 (13)	58 (12)
	Chemotherapy and trastuzumab	1 (< 1)	1 (<1)

pN1 or pN1mi	None	17 (7)	29 (6)
	Endocrine therapy	88 (35)	160 (31)
	Chemotherapy	32 (13)	48 (9)
	Endocrine and chemotherapy	115 (45)	259 (51)
	Chemotherapy and trastuzumab	1 (< 1)	15 (3)
pN2 or pN3	None	7 (4)	12 (5)
	Endocrine therapy	45 (28)	58 (25)
	Chemotherapy	22 (14)	41 (18)
	Endocrine and chemotherapy	83 (52)	121 (52)
	Chemotherapy and trastuzumab	2 (1)	12 (5)

Abbreviations: ALND= axillary lymph node dissection
SNB= sentinel lymph node biopsy

7.5 Follow-up

The median follow-up was 57 months in Study I, 89 months in Study II, 78 months in Study III and 52 months in Study IV calculated from the date of surgery. Planned follow-up visits took place at one, three and five years after breast surgery. In addition, the study participants had access to a hospital outpatient unit whenever there was concern of cancer recurrence. Physical examination, blood cell counts and blood chemistry and a bilateral mammography with or without breast ultrasound examination were performed at the planned visits and whenever considered indicated. When a recurrence was suspected, an isotope bone scan and computed tomography were usually carried out as the initial staging examinations. After the first five years, follow-up was continued at a local health-care centre or at a private health-care company based on patient preference.

Data on cancer recurrence and survival were collected from the hospital records and registries, and the database of the Finnish Cancer Registry. The database has coverage close to 100% (Teppo et al. 1985).

7.6 Statistical analysis

The time to LR after BCT or mastectomy was computed from the date of breast surgery to the date of LR diagnosis. LR was defined as any cancer recurrence in the ipsilateral breast after BTC or in the ipsilateral thoracic wall after mastectomy and LRR as any cancer recurrence in the ipsilateral thoracic wall, in the regional lymphatics or in both (Studies I and II). LR-free survival was calculated from the date of breast surgery to the date of first detection of LR, censoring patients who did not have LR on the date of the last follow-up visit or the date of death (Study II).

The medians were compared using the Mann-Whitney U-test (Study III). The estimates for LR, RR, AR and SR were computed using the Kaplan-Meier method. RR included AR, SR or parasternal recurrence, whichever occurred first.

Breast cancer-specific survival (BCSS) was calculated from the date of surgery to the date of death considered to be caused by breast cancer, censoring patients who were alive and those who died from an intercurrent cause. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause, censoring patients who were alive on the date of the last follow-up visit. Life tables were constructed according to the Kaplan-Meier method, and the survival and incidence of recurrences between the groups were compared with the log-rank test and the Cox multivariate proportional hazards model. P-values < 0.05 were considered statistically significant.

7.7 Breast imaging (Study IV)

MRI was performed on patients with Paget´s disease with negative findings on mammography and ultrasound since the year 1999. Dynamic contrast-enhanced MRI was performed using 1T or 1.5T systems. The MRI images were assessed by general radiologists until the year 2006 and by breast radiologists thereafter. Negative breast MRI images were re-evaluated by an expert breast radiologist. The re-evaluation was not performed blindly.

8. Results

8.1 Local recurrences after breast-conserving surgery (Study I)

Cancer recurrence and survival events

LR after BCT was detected in 27 of the 1297 study patients. LR was located at the previous resection site in 17 patients and outside the quadrant of the prior resection in the remaining 10 cases. The median time from surgery to an LR was 41(range 6-78) months regardless of the location of the recurrence. The 5-year cumulative LR incidence was 2.1%. Contralateral breast cancer was detected in 14 patients, none of whom were diagnosed with an LR. The median time from surgery to the date of the diagnosis of contralateral breast cancer was 34(range 10-61) months.

Only five patients had an ipsilateral AR (isolated AR, n = 1; LR and AR, n = 2; AR and concomitant distant recurrence, n = 2). Three patients had a nodal recurrence in the contralateral axilla. LR preceded contralateral AR in one of these three cases. One patient had an SR and one a parasternal recurrence (Table 5).

Distant metastases were detected in two patients (7%) with an LR and in 55 patients (4%) who did not have an LR. Three patients had contralateral breast cancer prior to or concomitantly with distant metastases. Thirty-two patients (2.5%) died from breast cancer during the follow-up, 15 (1.2%) from a cause other than cancer and in 9 (0.7%) from unknown cause (Table 5).

LR and age

Patients between 54 and 70 years at diagnosis had a lower 5- year LR incidence (1.0%) with an HR of 0.244 (95% CI 0.082-0.727), when compared with patients older than 70 years)univariate p= 0.011).

Table 5. Events observed in the 1297 patients treated with breast conservation (Study I).

Event	N
Cancer recurrence site	
Ipsilateral breast	27 (2.1%)
Contralateral breast	14 (1.1%)
Ipsilateral axilla	5 (0.5%)
Contralateral axilla	3 (0.2%)
Subclavicular nodes	1 (0.1%)
Parasternal nodes	1 (0.1%)
Distant metastases	57 (4.4%)
Death, breast cancer	32 (2.5%)
Death, other	15 (1.2%)
Death, unknown cause	9 (0.7%)

LR and radiotherapy

LRs were more frequent (5-year LR incidence of 13.7%) in patients who did not receive breast radiotherapy. The HR for LR was 11.2 (95% CI 2.5-51.0; p=0.002) in these patients, compared with those who received radiotherapy and a booster dose.

Radiotherapy was omitted in 30 patients due to fragility or co-morbidities or for an unknown reason (n = 1). Two (6%) of these 31 patients had an LR. Three (27%) of the 11 patients who refused the recommended radiotherapy had an LR; none of these 3 patients completed the recommended systemic therapy either.

Breast radiotherapy was not significantly associated with a lower incidence of cancer recurrence at the site of the previous resection (p= 0.491). The 5-year LR incidence outside the quadrant of the previous resection was 11.3% in patients without radiotherapy, 0.7% in patients with radiotherapy without a booster dose and 0.5% in patients who received a booster dose. The HR was 25.0 (95% CI 2.5-248.9; p <0.0001) for patients without radiotherapy as compared with those with radiotherapy and an additional booster.

LR and systemic adjuvant treatment

Administration of systemic adjuvant treatment was not significantly associated with LR incidence.

LR and histological and biological tumour features

Histological tumour type or grade, presence of EIC or tumour multifocality, tumour ER status, tumour HER2 status or the proliferation index MIB-1 were not risk factors for LR when evaluated separately. We were able to classify 1281 (99%) of the 1297 tumours into biological subtypes. Twenty-three tumours (1.8%) were ER-/HER2+ (HER2-enriched), 80 (6.2%) triple negative, i.e. ER-, PR-, HER2- (basal-type), and 1178 (92%) ER+ and either HER2+ (luminal B) or HER2- (luminal A). The 5-year LR incidence tended to be higher among patients with ER-/HER2+, i.e. the HER2-enriched subtype, than among patients with the other subtypes (p =0.074).

Multivariate analysis

The three most significant risk factors for LR in a univariable analysis were omission of radiotherapy, age at diagnosis and the biological tumour subtype. When these factors were entered into a Cox multivariate model as co-variables, omission of radiotherapy (HR 10.344; 95% CI 1.904-56.184; p= 0.007) increased the risk of LR. The biological subtype ER+HER2+/- was associated with a lower LR risk (HR 0.215; 95% CI 0.049-0.935; p= 0.040) when compared with the ER-HER2+ biological type.

8.2 Local recurrences after mastectomy (Study II)

Cancer recurrences and survival

The median follow-up time was 89 (range 2-130) months. Twenty-two patients (2.9%) had LR and 34 (4.5%) LRR during the follow-up. The 7-year LR incidence was 3.1% and LRR incidence 4.6%. The median time from surgery to LR was 27 (range 1-87) months and to LRR 29 (range 2-130) months.

Seven patients (0.9%) had a recurrence in the ipsilateral axilla. Two of these patients had concomitantly LR in the ipsilateral thoracic wall. The median time to recurrence in the ipsilateral axilla was 48 (range, 13-124) months. Ipsilateral SR was found in 8 patients(1.1%), concomitantly with an LR in one patient. The median time to SR was 28 (range, 1-59) months.

Contralateral breast cancer was detected in 35 patients (4.6%).

Distant metastases were diagnosed in 133 patients (17.6%). Distant metastases as the first event (without an LRR) occurred in 113 patients (15.0%). Eleven (50%) of the 22 patients with an LR had distant metastases. Two patients had distant metastases diagnosed prior to LR, four patients concomitantly with LR and five patients after detection of LR.

The 7-year BCSS was 85.9% and OS 74.5%. A total of 114 patients (15.1%) died from breast cancer and 100 patients (13.2%) from an intercurrent or unknown cause.

Risk factors for LR

Patients with PR-negative cancer had a 4.9% 7-year risk for LR as compared with a 1.8% risk in patients with PR-positive tumour in a univariate survival analysis ($p = 0.015$). Patients with ER-negative breast cancer tended to have a greater risk compared with patients with ER-positive cancer (6.0% vs. 2.4%, $p = 0.059$). Biological tumour groups formed by tumour ER and HER2 expression also tended to be associated with LR. Patients with either the ER-, HER2+ phenotype (9.5%) or the ER-, HER2- phenotype (4.9%) had a higher risk than those with the ER+, HER2- (2.1%) and the ER+, HER2+ (2.3%) phenotypes ($p = 0.056$). However, none of these three factors (PR, ER, biological group) were independent risk factors for LRs in the multivariable analysis.

Radiotherapy had no significant effect on LRs, not even when patients were analysed according to lymph node status. In N0 patients, the 7-year LR rate was 3.1% in 281 patients without radiotherapy and 1.7% in 57 patients with radiotherapy ($p=0.763$). In N1 patients, the 7-year LR rate was 5.2% in 14 patients without radiotherapy and 1.8% in 173 patients with radiotherapy ($p=0.628$). The 7-year LR rate was 4.9% in 138 N2-N3 patients who received radiotherapy and 25% in 21 N2-N3 patients without radiotherapy ($p= 0.628$). N2-N3 nodal stage was an indication for both radiotherapy and chemotherapy, but 21 patients did not receive radiotherapy. Nine patients (43%) who did not receive radiotherapy were older than 85 years, while two patients refused radiotherapy. The median age of N2-N3 patients treated without radiotherapy was 74 years compared with 58 years in N2-N3 patients who received radiotherapy ($p=0.004$). Also the N2-N3 patients who did not receive chemotherapy were older (median 78 years) than those who had chemotherapy (median 52 years) ($p>0.0001$).

The other studied factors, comprising age at diagnosis, tumour site in the breast, tumour histological type or grade, axillary lymph node status or administration of systemic adjuvant treatment, were not associated with LR rate.

Survival after LR

The 7-year BCSS rate was 86.9% in patients without LR, while it was 56.7% in patients with LR ($p < 0.0001$). The 7-year overall survival figures were 75.7% and 45.5%, respectively ($p = 0.001$). The median follow-up time after LR was 38 (range 1-103) months. The 5-year BCSS survival rate after LR, as calculated from the date of LR, was 54.8%, and the 5-year OS was 42.5%.

Sixteen (72.7%) of the 22 patients with LR did not have prior or concomitant distant recurrence. Five (31.3%) of these 16 patients developed distant metastases after detection of the LR during a median follow-up of 61 (range 1-103) months, and three died from breast cancer and three from an intercurrent cause during the follow-up. The 5-year BCSS and OS rates of the 16 patients with isolated chest wall recurrence were 77.5% and 59.2%, respectively, as calculated from the date of detection of the LR. The six patients who had distant metastases diagnosed either prior to or simultaneously with LR died from breast cancer within 1 to 14 months after detection of the chest wall recurrence.

8.3 Axillary and supraclavicular recurrences after ALND (Study III)

Events

AR was observed in eight patients (0.7%) and SR in 14 patients (1.2%). The median time to AR was 11.5 (range 5-60) months and to SR 39 (range 14-61) months. The cumulative 7-year AR incidence was 0.7% and SR incidence 1.3%.

Only one patient presented with an isolated AR. The remaining seven AR patients had concomitant LR or distant recurrences. Three of them also had either concomitant or subsequent SR. Five of the eight patients with AR died of breast cancer during the follow-up. All SR patients had other local, regional or distant recurrences concomitantly with SR. Twelve patients had distant metastases concomitantly with SR. Distant metastases preceded SR in one patient, while another patient had distant metastases 11 months after SR. Altogether 11 out of 14 patients with SR died of breast cancer.

Only one patient had parasternal nodal recurrence. This recurrence was isolated, without other local, regional or distant recurrences. The patient was alive at the end of follow-up.

Altogether seven patients (0.6%) had contralateral regional recurrence [AR (n= 5) or SR (n=2)] without contralateral breast cancer. Two of the five patients with contralateral AR were alive at the end of follow-up. In one patient, LR preceded the contralateral AR; the other patient had concomitant distant metastases and also LR two years later. Three patients with contralateral AR died of breast cancer. The two patients with contralateral SR had subsequent distant metastases, but were alive at the end of follow-up.

LR was observed during the follow-up in 21 patients (3.8%) with BCT and in 20 patients (3.2%) with mastectomy. Contralateral breast cancer was detected in 54 patients (4.6%). Distant metastases were observed in 177 patients (15.0%). In 137 of these patients, distant metastases without concomitant LRR were the first observed event. Altogether 128 patients (10.8%) died of breast cancer. The cause of death was unknown or other than breast cancer in 108 patients (9.2%). The 7-year BCSS was 88.8% and OS 80.7% for the entire study population.

Risk factors for AR

The cumulative AR incidence at 7 years was 2.1% (n=4) in N2-N3 patients, 0.8% (n=3) in N1 patients and 0.2% (n=1) in node-negative patients. None of the patients with micrometastasis had AR (p=0.079). The median number of examined axillary nodes was 13 (range 9-20) in patients with AR and 15 (range 6-52) in patients without AR (p=0.151). In patients with N1-N3 disease, the median number of positive nodes was 4 (range 1-15) in those with AR and 2 (range 1-31) in those without AR (p= 0.193). The median proportion of positive nodes of the examined nodes was 23% (range 8-88%) in patients with AR and 15% (range 3-100%) in patients without AR (p=0.381).

Patient age, tumour localization, tumour histological type and grade, HER-2 status, ER or PR status or systemic adjuvant treatment given had no influence on AR rate, also when studied separately in N1 and N2-N3 patients.

Risk factors for SR

The 7-year SR incidence was 2.1% (n=4) in N2-N3 patients, 1.1% (n=4) in N1 patients, 2.1% (n=2) in N1mi patients and 0.9% (n=4) in node-negative patients (p=0.579). The median number of examined axillary nodes was 15 both in patients with and without SR (p= 0.958). Among N1-N3 patients, the median number of metastatic nodes was 3.5 (range 1-27) in SR patients and 2 (range 1-31) in patients without SR (p= 0.802). Among SR patients, the median proportion of positive nodes of the examined nodes was 21% (range 6-95%), while it was 15% (range 3-100%) among those without SR (p=0.786).

Patients with histological grade III tumour had a 7-year SR incidence of 2.2%, which was higher than the 1.6% observed among patients with grade II tumours. None of the patients with grade I tumours had SRs. The difference was significant (p= 0.031). Patients with ER-positive tumours had a lower SR rate (0.9%) than the 3.4% in patients with ER-negative tumours (p=0.009). Also patients with PR-negative tumours had SRs more often (2.5%) than patients with PR-positive tumours (0.6%; p= 0.003). Systemic adjuvant treatment, patient age, tumour localization, T-stage, tumour histological type or grade or HER-2 status had no effect on SRs.

When N1 and N2-N3 patients were analysed separately, no significant risk factors were observed in N1 patients. In N2-N3 patients, the only significant risk factor for SR was PR-negative tumour (SR incidence of 5.6%, compared with 0% in patients with PR-positive tumour; p=0.010).

Influence of AR and SR on survival

In patients without AR the 7-year BCSS was 89.2 and OS 81%, while these were 33.3 and 33.3% in patients with AR (log-rank p <0.0001 for both BCSS and OS). The 7-year BCSS was 89.7 and OS 81.5% in patients without SR, and 17.9 and 17.9% in patients with SR, (log-rank p <0.0001 for both BCSS and OS).

In univariate analysis, significant prognostic factors for BCSS included N-stage, both ER and PR status, T-stage, AR and SR (p<0.0001 for all factors). The same factors predicted OS in univariate analysis with the same statistical significance. In addition, patient age over 50 years was related to poor OS (p< 0.0001).

In multivariate analysis, SR was an independent risk factor for poor BCSS (HR 10.1; 95% CI 4.5-23.0; p<0.0001). Also N2-N3 nodal stage (p<0.0001) and T2-4 T-stage (p<0.0001) were significant predictors for worse BCSS. The independent risk factors for poor OS included SR (HR 5.8; 95% CI 2.7-12.3), N2-N3 nodal stage, T2-4 tumour histological stage and also patient age over 50 years (p<0.0001 for all factors). Unlike SR, AR was not an independent risk factor for BCSS (HR 1.0; 95% CI 0.03-3.2; p=0.984) or for OS (HR 1.1; 95% CI 0.4-3.3; p=0.863).

Selective use of radiotherapy in N1 patients

The N1 patients with or without regional radiotherapy were similar regarding the T-stage, histological grade, ER status, PR status and HER-2 status (p =0.235 or larger for all variables). Regional radiotherapy was given significantly more often to younger patients. It was given to 94 (90%) of the 104 patients who were aged 50 years or younger, compared with 207 (74%) of the 280 patients who were older than 50 years (p= 0.002). Chemotherapy was given to 34 (42%) of the 83 patients without regional radiotherapy, compared with 214 (71%) of the 301 patients who received regional radiotherapy (p<0.0001). Altogether 139 (73%) of the 190 patients with a single axillary metastasis received regional radiotherapy, which was less frequent than the 101 (86%) of 124 patients with two positive nodes or the 61 (87%) of 70 patients with three positive nodes, but the difference was not significant (p= 0.107).

Regional radiotherapy in N1-N3 patients

The regional radiotherapy fields varied markedly between study patients. The N1 and N2-N3 patients were divided into three groups: patients without radiotherapy, those with local radiotherapy only and those with local radiotherapy and radiotherapy to the axillary or supraclavicular nodal basins. Regional recurrence included ipsilateral SR, AR and parasternal recurrences, whichever occurred first. The influence of the extent of radiotherapy on LR, distant metastases and regional recurrence was evaluated.

The 7-year regional recurrence incidence was 2.2% in the 53 N1 patients without radiotherapy, 0% in the 30 N1 patients with local radiotherapy and 2.3% in the 301 N1 patients with local-regional radiotherapy (p=0.739). The 7-year incidences of distant metastases were 15.8%, 10.9% and 14.7%, respectively (p=0.807). However, the 7-year LR rate was significantly lower in patients who received local (0%) or local-regional radiotherapy (2.6%), compared with 11.6% in patients without radiotherapy (p=0.005).

Among N2-N3 patients, the cumulative 7-year regional recurrence incidence was 34.3% in the 28 N2-N3 patients without radiotherapy, 0% in the 12 N2-N3 patients with local radiotherapy only and 1.2% in the 190 N2-N3 patients with local-regional radiotherapy (p<0.0001). The 7-year incidence of LRs and distant metastases were 27.0% and 59.6% in patients without radiotherapy, 0% and 68.2% in patients with local radiotherapy and 3.5% and 35.0% in patients with local and regional radiotherapy (p= 0.011 for LR and p=0.029 for distant metastases). Two N2-N3 patients received radiotherapy only to the regional nodal basins.

8.4 Patients with Paget´s disease of the breast (Study IV)

Preoperative findings in clinical examination and breast imaging

Altogether 20 (19 with invasive cancer and one with DCIS) out of 58 patients with Paget´s disease had palpable tumours. No tumours in breast palpation were detected in the two patients with Paget´s disease only, in the 22 patients with DCIS and in the eight patients with invasive cancer. This information was missing for six patients. Ten patients underwent mammography only and two patients ultrasound examination only, while both examinations were performed on 42 patients. Data regarding breast imaging were missing for four patients. The sensitivity of mammography and ultrasound was 28/22 (79%) and 23/17 (74%) in invasive cancer and 23/9 (39%) and 21/4 (19%) in DCIS, respectively.

Fourteen patients underwent breast MRI. Twelve of these 14 patients had no suspicious lesions in mammography and ultrasound. Altogether seven of the 14 patients had malignant or suspicious findings in MRI, either according to the original interpretation or after the re-evaluation. The re-evaluation of the MRI images revealed false-negative interpretations in two cases, both in patients with underlying DCIS. Five of the seven MRI-positive patients, three with underlying DCIS and two with invasive carcinoma, had no suspicious findings in mammography and ultrasound. The sensitivity of MRI was 100% in invasive cancer and 44% in DCIS.

Surgery

Treatment of the 58 patients with Paget´s disease is summarized in Table 6. The two patients with Paget´s disease only underwent central resection. Fourteen DCIS patients and three patients with invasive cancer underwent central resection as primary surgery. Five patients with breast conservation (two of them with DCIS) had mastectomy as a second operation. Eleven DCIS patients and 28 patients with invasive cancer underwent mastectomy as primary surgery. The overall mastectomy rate was 76%. The proportion of patients with mastectomy was constant during the study period.

No axillary surgery was performed in 14 patients, including both patients with Paget´s disease only and 12 patients with pure DCIS. Six patients with pure DCIS underwent SNB, all with negative findings. Level I-II ALND was performed on two patients with microinvasive DCIS, both with invasive cancer as the preoperative diagnosis. One of these two patients had a lymph node metastasis in her ALND specimen. Five patients with DCIS, including the third patient with microinvasive DCIS, underwent partial level I lymph node dissection.

Nineteen patients with invasive cancer underwent ALND without preceding SNB. Six were node negative. Twelve patients with invasive cancer underwent SNB, seven of them with tumour-negative findings. ALND was performed on four patients with tumour-positive SNB and in one patient with negative SNB findings because of multifocal cancer. All four patients with tumour-positive SNB had additional metastases in their ALND specimens. ALND was omitted in one 95-year-old patient with invasive cancer and positive SNB findings.

Adjuvant treatment

Adjuvant radiotherapy was given to 20 patients. Three patients received breast radiotherapy after central resection, with a booster dose to the tumour bed in one patient. The remaining 17 patients received post-mastectomy radiotherapy. Three patients with invasive cancer and one patient with extensive pure DCIS received radiotherapy to the thoracic wall only. Twelve patients with invasive cancer and one patient with microinvasive DCIS and axillary lymph node metastasis received radiotherapy also to the axilla and the supraclavicular nodes.

Systemic adjuvant therapy was given to 23 patients, all with invasive cancer. Nine patients received endocrine therapy only, nine patients chemotherapy only and five patients received both chemotherapy and endocrine therapy.

Table 6. Treatment of the 58 patients with Paget's disease of the breast (Study IV).

	Paget´s disease only (N=2)	DCIS (N=25)	Invasive cancer (N=31)
Primary breast surgery			
Central resection	2	14	3
Mastectomy	0	11	28
Mastectomy as reoperation			
	0	2	3
Axillary surgery			
None	2	12	0
SNB	0	6	7
SNB and ALND	0	0	5
partial ALND	0	5	0
ALND	0	2	19
Radiotherapy			
Breast only	0	3	0
Thoracic wall only	0	1	3
Thoracic wall and regional nodes	0	1	12
Systemic adjuvant treatment			
None	2	25	8
Endocrine only	0	0	9
Chemotherapy only	0	0	9
Endocrine and chemotherapy	0	0	5

DCIS = ductal carcinoma in situ, SNB= sentinel node biopsy, ALND= axillary lymph node dissection

Histological findings

Altogether 56 patients (97%) had underlying invasive or in situ carcinoma in the ipsilateral breast, while two patients had Paget´s disease only. Thirty-one patients (53%) had invasive cancer. Extensive intraductal component was detected in 12 of the 31 patients with invasive cancer. Three patients (5%) had microinvasive and 22 patients (38%) had pure DCIS. The underlying DCIS was high-nuclear grade in 17 patients, intermediate-nuclear grade in four patients and low-grade in four patients.

The tumour characteristics, including multicentricity and multifocality, locations and pathological T- and N-stages, are presented in Table 2 on page 26.

Local, regional and distant recurrences

The median follow-up was 52 (range 1-158) months. No LRs were detected after mastectomy. LR was detected in one patient 10 months after central resection. Preoperatively, she had no findings on mammography, ultrasound or MRI. The histopathological assessment of the surgical specimen revealed a 10 mm DCIS. She received no radiotherapy. The histopathological evaluation of the salvage mastectomy specimen revealed bifocal invasive recurrence. SNB with tumour-negative findings was also performed during salvage surgery. The patient was free of further recurrences after a follow-up period of seven years.

One patient had isolated AR after negative findings on SNB. She underwent ALND as salvage surgery, with a metastasis in 1 of the 15 examined axillary lymph nodes. She was free of recurrences 28 months after salvage surgery. No ARs were detected in patients with ALND or in those without axillary surgery. Two patients (8%) with ALND had a recurrence in the supraclavicular lymph nodes, concomitant with distant metastases. Distant metastases during follow-up were found altogether in six patients (10%), all with preceding invasive breast cancer. Ten patients (17%) died during the follow-up, four (7%) of breast cancer, two (3%) of coronary heart disease and four (7%) of unknown causes.

The 5-year recurrence-free survival was 90% in patients with DCIS and 63% in those with invasive cancer. The five-year OS was 94% and 73%, respectively.

9. Discussion

9.1 Ipsilateral breast recurrence after breast conserving surgery

The low LR rate found in this study is in good agreement with the annual rate of ipsilateral recurrence of approximately 0.5% reported in recent studies (Millar et al. 2009, Sanghani et al. 2010). The majority of LRs are diagnosed within the first five years after surgery (EBCTCG 2005a), and presumably the LRs at the previous resection site should occur earlier than those outside the quadrant of the primary tumour (Freedman et al. 2005). In the present study, the median time to an LR was similar regardless of the site of the recurrence, and approximately two-thirds of LRs occurred at the prior resection site (in the same quadrant) and were considered “true recurrences”. Usually LRs outside the quadrant of the primary tumour are considered to be second breast cancers developed de novo or missed multicentric cancers. Nevertheless, we found recurrences outside of the quadrant of the previous resection to arise nearly as frequently as contralateral breast cancers.

As expected, breast radiotherapy reduced LRs, but somewhat unexpectedly the effect appeared to be limited to recurrences located outside the quadrant of the prior resection. The reasons for the presumably undetected effect of radiotherapy on the rate of recurrences occurring at the prior resection site may be the relatively wide resections performed at our unit. Also the retrospective, non-randomized study setting may bias our findings.

After BCT, radiotherapy offers both a reduction of LRs and a survival benefit, although the absolute benefit varies substantially according to the patient and tumour characteristics (EBCTCG 2011). In previous studies dating back to the 1980s (EBCTCG 2005a) and the 1990s (Holli et al. 2001), the LR rates have been higher, even with radiotherapy, than in this study. The 5-year LR risk after breast-conserving surgery and radiotherapy was 7% in the EBCTCG overview (2005a), compared with 2.1% in the present study with only pT1 breast cancer patients. In the Finnish trial, patients with even more favourable prognostic features, i.e. small (≤2 cm), node-negative, low cell proliferation rate, PR-positive tumours resected with a minimum margin of 1 cm, were randomized to BCT with or without adjuvant radiotherapy (Holli et al. 2001). The LR rate was 7.5% after adjuvant radiotherapy during a follow-up of 6.7 years. It is noteworthy that the study patients received no systemic treatment (Holli et al. 2001). In our study, 65% of patients received adjuvant systemic treatment.

Radiotherapy can also worsen the final aesthetic outcome and has adverse effects, which are more common in elderly patients. The elderly are also more likely to have serious co-morbidities and do not benefit from radiotherapy as much as younger patients (EBCTCG 2005a). Omitting radiotherapy after breast conservation seems to be safe in elderly patients (over 70 years) with small hormone receptor-positive cancers treated with adjuvant tamoxifen (Hughes et al. 2004). We observed LRs relatively often (5.9%) in patients over 70 years treated without radiotherapy, despite 82% of these women receiving adjuvant endocrine therapy. However, the LRs were particularly frequent among the few patients who refused radiotherapy. Of note, all three LR patients who had refused radiotherapy had also refused or discontinued systemic adjuvant treatments.

Partial-breast irradiation is being investigated in several ongoing studies (Smith et al. 2012, Sperk et al. 2012). The results have been mainly encouraging, but are preliminary and have a short follow-up. The TARGIT trial reports an excellent short-term outcome with intraoperative partial-breast irradiation (Sperk et al. 2012). On the other hand, partial-breast radiotherapy was associated not only with increased risk of subsequent mastectomy but also with more complications compared with traditional whole-breast radiotherapy in older women (Smith et al. 2012). Furthermore, the results of the ACOSOG Z0011 trial suggest that ALND can be avoided in patients with sentinel lymph node metastases when whole-breast radiotherapy after BCT is given (Gentilini et al. 2011), favouring whole-breast radiation rather than partial breast radiotherapy. Nevertheless, more evidence is needed regarding the indication and use of partial-breast irradiation techniques before being recommended to patients outside clinical trials.

9.2 Local recurrence after mastectomy

Ipsilateral chest wall recurrences were infrequent after mastectomy in this series of breast cancer patients, who were frequently treated also with post-operative radiotherapy and systemic adjuvant therapies. Somewhat surprisingly the 7-year LR rate was low even in patients with N2 or N3 nodal status, 4.5%, or in patients with T3 or T4 tumours, 6.6% and 4.8%, respectively. In the EBCTCG overview (2005a), the LR rates were substantially higher, 12% in N2-3 patients with post-mastectomy radiotherapy and 26% in N2-3 patients without radiotherapy in five years. However, the studies included in the overview date back to when radiotherapy techniques were suboptimal and the available adjuvant systemic treatments were both less effective and less frequently used.

Apart from radiotherapy and systemic adjuvant treatments, also the quality of surgery and pathological assessment of the surgical specimens are likely of key importance. In the Helsinki metropolitan area, centralization of breast cancer surgery has markedly improved the quality of both surgery and breast pathology.

LRs after mastectomy have been related to unfavourable histological and biological tumour features, such as high histological tumour grade or absence of steroid hormone receptors (Taras et al. 2011, Trovo et al. 2012). No such risk factors were identified in our study. However, in the univariate analysis, PR negativity was significantly associated with an increased risk for LR. Also tumour ER-negativity and the ER-/HER2- and ER-/HER2+ biological subtypes showed a similar tendency. Yet, none of these factors had an independent influence on the risk in the multivariate analysis. These findings need to be viewed with some caution, however, since the number of LRs was small despite the relatively large size of the cohort. The small number of events coupled with administration of adjuvant treatments tailored to the patient risk profile may have prevented detection of some clinically important associations.

Young women have more LRs than older women, also after mastectomy (Yildirim and Berberoglu 2007). In the present study, the 7-year LR rate was 6.5% in patients aged under 40 years at the time of breast cancer diagnosis compared with 2.5-3.3% in older patients. In two recent studies of patients who had pN0 or pN1 cancer and who received no post-mastectomy radiotherapy, LRRs were related to young age (Sharma et al. 2010) and premenopausal status (Trovo et al. 2012). At the same time, younger patients are often good candidates for immediate breast reconstruction. Still a delayed reconstruction might be a better option if post-mastectomy radiotherapy is probable. Post-mastectomy radiotherapy after breast reconstruction is associated with more post-operative problems such as impaired cosmesis or even risk of losing the reconstruction, especially when implants are used (Berry et al. 2010). Autologous flaps tolerate radiation better, but radiotherapy may cause fibrosis and have an adverse effect on the aesthetic outcome also in flap reconstruction (Tran et al. 2000).

The outcome of patients with LR after mastectomy has been regarded as bleak, and also in the present series LR was associated with a survival disadvantage. Patients with an isolated LR have a better prognosis; the 5-year BCSS is 77.5% and OS 59.2%, as calculated from the date of detection of the chest wall recurrence, compared with 54.8% and 42.5%, respectively, in all the patients with LR.

The prognosis of patients with an isolated LR may be improving; apart from our study, another recent study reported a better 5-year OS, 66.4% (Chen et al 2009), compared with 43-44% in older studies (Chapgar et al. 2004, Nielsen et al. 2006). However, conclusions need to be drawn with caution. It is not known whether the biological aggressiveness of the LRs that are not prevented by modern adjuvant treatments is similar to the LRs that surface when solely local therapies are given.

9.3 Axillary and supraclavicular recurrences after ALND

The study confirmed the very low risk of AR or SR after ALND. ARs were so rare that no risk factors could be identified. A more recent study with 4473 patients found patient age under 40 years, medially located tumour, only level I ALND performed and absence of endocrine therapy to be associated with increased risk of ARs (Shen et al. 2012). All of our patients underwent level I-II ALND and even level III dissection whenever suspicious nodes on level II or III were observed during surgery. We did not analyse the possible influence of tumour location in the breast.

AR was not an independent risk factor for poor survival, but the 7-year BCSS and OS were low, both 33.3% in patients with AR. Only one patient had isolated AR without concomitant distant or local disease. Another study reported a better survival, a 10-year BCSS of 51.4% in patients with AR, but the majority of these patients (77%) had isolated ARs (Shen et al. 2012). Unlike ARs, SRs were associated with aggressive disease, i.e. grade III and hormone-receptor negative tumours. SR was also related to poor survival despite the relatively short follow-up.

Some studies have shown higher regional recurrence rates among patients with numerous metastatic nodes or with a high proportion of involved nodes (Grills et al. 2003, Truong et al. 2009) but in our no such association was identified. Furthermore, six of the 14 SR patients were node negative or had micrometastases only.

Regional radiotherapy reduces regional recurrences (Voogd et al. 2001, Truong et al. 2009) but is associated with serious morbidities such as lymphoedema, brachial plexopathy or radiation pneumonitis (Fathers et al. 2002, Christensen et al. 2008, Tsai et al. 2009). Abundant controversy exists concerning which patient population benefits from regional radiotherapy despite the associated morbidity. In this study, regional radiotherapy was often omitted in N1 and N2-N3 patients due to fragility and serious co-morbidities. The omission of regional radiotherapy was a risk factor for regional recurrence in N2-N3 patients, but not in N1 patients, although N2-N3 patients without regional radiotherapy were at least as highly selected as those with N1 nodal stage. Also distant metastases were less common in N2-N3 patients receiving regional radiotherapy, while in N1 patients the use of radiotherapy had no influence on distant metastases. However, conclusions regarding the impact of regional radiotherapy on survival are not justified due to the non-randomized study setting and the relatively short follow-up.

At the Helsinki University Central Hospital Department of Oncology, regional radiotherapy was recommended for all N1 patients until 2001. Thereafter, the use of regional radiotherapy in N1 patients has gradually decreased. Currently, regional radiotherapy is recommended only for N1 patients with extranodal extension of axillary metastasis, but for all N2-N3 patients.

9.4 Local recurrences and survival

In the EBCTCG overview (2005a), patients with breast conservation as well as node-positive patients with mastectomy had less recurrences and also better survival when radiotherapy was used. However, the reduction of LRs may not translate into better survival in all patients. In node-negative patients with mastectomy, radiotherapy reduced the LR rate, but survival was not improved (EBCTCG 2005a). In addition, if the patient´s risk for LR was estimated to be low, i.e. less than 10%, there was no benefit from fewer LRs in terms of survival.

A Danish study evaluated survival after mastectomy with and without radiotherapy (Kyndi et al. 2009). In that study, the reduction of LRs was highest in the "high-risk" group when post-mastectomy radiotherapy was used, but without survival benefit. On the other hand, in the "low-risk" group, the 11% absolute reduction in LRs after post-mastectomy radiotherapy provided an 11% absolute reduction in 15-year breast cancer mortality (Kyndi et al. 2009). This subgroup of patients had a significantly higher survival benefit from preventing LRs than that found in the EBCTCG overview in 2005.

In the Danish study patients treated during the 1980s, the "high-risk" group had an extremely poor prognosis with just 19% disease-specific survival at 15 years. Although better local control was achieved in these "high-risk" patients, the survival did not improve because of a lack of efficient treatment to eradicate distant disease.

The survival benefit from local control seems to be related to the tumour stage and also to tumour biology. Patients who have aggressive tumours with high metastatic potential and resistance to systemic treatments may benefit from radical local treatment when diagnosed at an early stage. Today, the more effective systemic adjuvant treatments may be helpful in high-risk patients in eradicating systemic disease, thus increasing the number of patients benefiting from better local control compared with patients treated in the 1980s. Besides the achievements in systemic treatment, also radiotherapy techniques have improved. In view of this, together with the better quality of surgery and pathology, patients today might benefit from good local control more than patients treated in the 1980s, such as those included in the EBCTCG overview. However, an important goal in the future is to obtain more accurate knowledge about the behaviour of tumours with different molecular biology, which could help to target the treatments and to identify the subgroup of patients who benefit most from better local control, especially in terms of survival.

9.5 Evolution of surgical treatment and local-regional recurrences

In Western Europe and the US, the mammography screening programmes and improved imaging techniques in general allow detecting breast cancer at an early stage. The early detection improves not only the prognosis of patients but also their quality of life because mutilating operations, like mastectomy and ALND, can be avoided in a considerable proportion of patients.

The introduction of less invasive and mutilating procedures, such as breast conservation and SNB, has not led to an increased risk of LRR. This is due to improvements in the quality of surgery because of better education and training of breast surgeons, and also because of centralization. In addition, radiotherapy techniques have improved and current systemic adjuvant treatments are more frequently used and more effective, than in the past.

In general, the current multidisciplinary approach in the treatment of breast cancer enables tailoring breast surgery individually, minimizing the risk of LRRs and distant recurrences and maximizing the quality of life.

9.6 Paget´s disease of the breast

We found underlying invasive cancer in 53% and DCIS in 43% of patients with Paget´s disease, which is in accordance with earlier studies (Kothari et al. 2002, Kawase et al. 2005) and also a more recent study (Dominici et al. 2012). The proportion of multifocal or multicentric invasive tumours was quite high (58%), as reported also in another study (Kothari et al. 2002). A peripheral tumour location was detected in 81% of the patients with invasive cancer. On the other hand, most of our Paget´s patients with DCIS had centrally located and unifocal tumours.

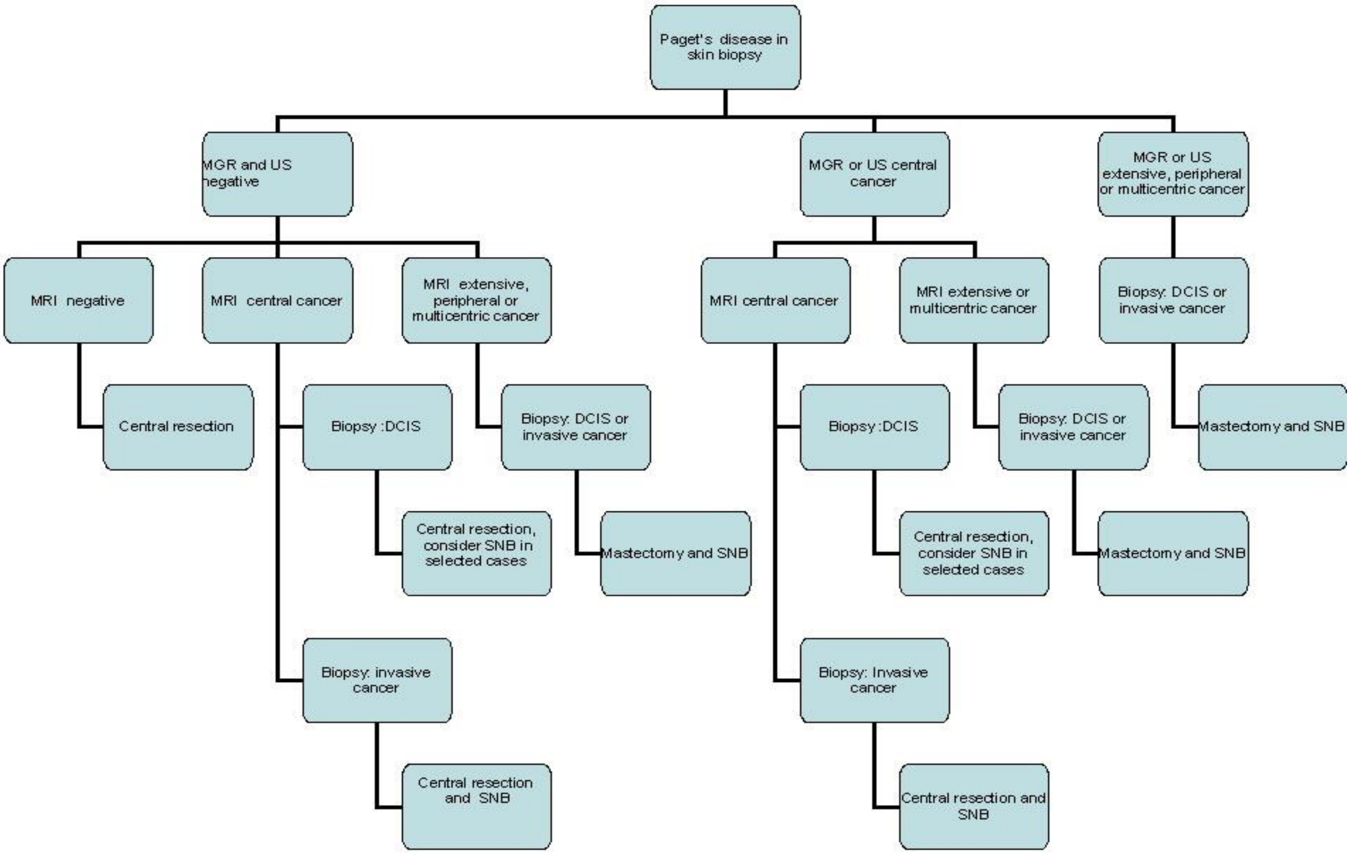
The sensitivity of mammography was just 39% in DCIS, but significantly higher, 79%, in invasive cancer. In previous reports, the proportion of Paget´s patients with negative mammography has varied between 22% and 84% (Bijker et al. 2001, Kothari et al. 2002, Marshall et al. 2003, Kawase et al. 2005, Sukumvanich et al. 2007). The sensitivity of MRI was better, 100%, in invasive cancer and 44% for DCIS. However, the MRI imaging was performed partially with out-of- date 1T equipment. Two other studies have demonstrated that MRI is useful in patients with Paget´s disease to detect mammographically occult disease (Dominici et al. 2012, Morrogh et al. 2008). Both recommend MRI for patients with Paget´s disease and a negative mammography.

Due to the high prevalence of peripheral and multicentric tumors not revealed in imaging, mastectomy has been considered the safest option for most Paget´s patients. However, a few studies have emphasized the feasibility of breast conservation in selected patients, mostly with negative mammography and/or MRI and without a palpable mass (Marshall et al. 2003, Dominici et al. 2012) or with limited disease (Bijker et al. 2001). Caliskan and colleagues consider breast conservation for all Paget´s patients as the first treatment option (2008).

No consensus exists regarding the use of SNB in Paget´s patients. Axillary nodal staging is recommended in these patients as in any other breast cancer patients (Laronga et al. 2006, Morrogh et al. 2008) or even in all Paget´s patients without any radiological findings (Caliskan et al. 2008, Sukumvanich et al. 2007). However, Paget´s patients without invasive cancer do not benefit from SNB and are exposed to unnecessary morbidity.

We created a treatment algorithm based on the findings of this study for patients with Paget´s disease of the breast on skin biopsy (Figure 1). Recently, another treatment algorithm for Paget´s patients was introduced by Dominici et al. (2012). Like us, they recommend breast MRI in all patients with negative findings in mammography. In addition to patients with negative mammography and breast ultrasound, we recommend MRI also when conventional imaging reveals only a central tumour and breast conservation is considered. Both algorithms recommend SNB in all patients undergoing mastectomy or when invasive cancer is detected. Moreover, both algorithms propose omission of SNB in case of central resection without prior evidence of invasive disease.

Figure 1.



Paget's disease in skin biopsy
MGR and US negative
MGR or US central cancer
MGR or US extensive, peripheral or multicentric cancer
MRI negative
MRI central cancer
MRI extensive, peripheral or multicentric cancer
MRI central cancer
MRI extensive or multicentric cancer
Biopsy: DCIS or invasive cancer
Central resection
Biopsy :DCIS
Biopsy: DCIS or invasive cancer
Biopsy :DCIS
Biopsy: DCIS or invasive cancer
Mastectomy and SNB
Central resection, consider SNB in selected cases
Mastectomy and SNB
Central resection, consider SNB in selected cases
Mastectomy and SNB
Biopsy: invasive cancer
Biopsy: Invasive cancer
Central resection and SNB
Central resection and SNB

10. Limitations of the study

The major limitation of this study lies in its retrospective, non-randomized study setting. This limitation concerns particularly evaluation of the effect of radiotherapy. Also the number of LRs was low despite the relatively large sizes of the cohorts. The small number of events coupled with administration of adjuvant treatments tailored to the patient risk profile may have prevented detection of some clinically important associations. Furthermore, the incidence of LRs after BCT was evaluated only in patients with pT1 tumours, and the median follow-up time of 57 months was relatively short for detecting LRs, particularly in ER+ tumours. On the other hand, the majority of breast conserving surgery is performed on patients with small tumours and the majority of LRs appear within the first five years after surgery (EBCTCG 2005a).

Other factors, such as patients' co-morbidities or surgeons' experience, may have also had an influence on LR rate but such factors were not evaluated here.

Only one patient with Paget´s disease had an LR during follow-up, allowing no comparison between patients with Paget´s disease and other breast cancer patients in this regard. Moreover, only fourteen patients (24%) with Paget´s disease underwent breast MRI, and this was partially done with out-of-date 1T breast MRI equipment. Thus, the role of MRI cannot be estimated reliably. We created a treatment algorithm for patients with Paget´s disease of the breast regarding the use of sentinel node biopsy and breast MRI imaging. However, our algorithm is based more on common sense that on evidence gained from this study.

11. Conclusions

Local and regional recurrences are rare after breast cancer surgery and modern multidisciplinary treatment, at least during a short follow-up. Paget´s disease is rather frequently associated with peripheral or multicentric cancer. Sentinel node biopsy is recommended in patients with Paget´s disease with invasive cancer or in case of mastectomy. Magnetic resonance imaging may be helpful in patients with Paget´s disease with negative findings in conventional imaging.

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